For decades, women’s health advocates have been concerned about the safety of Depo-Provera, the progesterone-based contraceptive shot (the shot). Some of the earliest concerns sparked by findings from animal studies have been laid to rest by carefully conducted clinical research, like studies showing that Depo does not increase women’s risk of breast cancer.\(^1\) The findings about Depo’s effect on women’s bone mineral density, however, continue to raise troubling questions about the safety of this drug. Women who use Depo experience a loss of bone mineral density (BMD), which may put them at higher risk for osteoporosis and bone fractures later in life.\(^2\) In a post-menopausal woman, a BMD loss of as little as 10 percent to 13 percent increases her fracture risk 1.4- to 2.6-fold.\(^2\)

The concern with respect to the shot is that, if a woman doesn’t regain her lost BMD after she stops using Depo, she may be more vulnerable to debilitating bone fractures. Women are already four times more likely than men to develop osteoporosis, and a drug for women that causes long-term BMD loss might increase that disparity. “Depot Medroxyprogesterone Acetate (DMPA), known as Depo-Provera, is a long-lasting contraceptive hormone that is 97-99.7% effective in preventing pregnancy. Depo-Provera contains synthetic progesterone and is given by injection, usually in the arm, hip, upper thigh, or abdomen. Each shot is effective for about 13 weeks. Depo Provera prevents the ovaries from releasing eggs, causes the cervical mucus to thicken, and changes the uterine lining — making it harder for sperm to enter and/or survive in the uterus and preventing fertilization. Depo Provera does not protect against sexually transmitted infections, including HIV. The method’s advantages include the fact that it is long-acting; is discreet and not obvious to others; does not contain estrogen or interrupt sex play; and may decrease the risk of ovarian and uterine cancers. In addition to BMD loss, the method’s disadvantages include a delay of the return of fertility, irregular bleeding, and weight gain. Some women also experience headaches, mood changes, and breast tenderness. It can take more than six months for Depo to clear the body, and side effects may linger until then.”

**Bone-Loss**

When Depo was approved for use in the U.S. in 1992, preliminary research indicated that women using it experienced bone mineral density losses that could lead to osteoporosis and fractures.\(^3\) The Food and Drug Administration (FDA) responded to this concern by requiring Depo’s manufacturer to conduct post-
approval studies to examine Depo’s effect on BMD. In 2004, data submitted to the FDA by Pfizer (which now owns Depo) showed that Depo did, in fact, have a harmful effect on bone density for some women, and the FDA changed the drug label to reflect these risks. The Depo label now includes a warning stating that:

Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. Depo-Provera Contraceptive Injection should be used as a long-term birth control method (e.g. longer than 2 years) only if other birth control methods are inadequate. Along with this warning, the drug’s patient insert describes detailed results from the studies in which bone loss was observed among Depo-Provera users, and suggests that patients who continue using the shot for longer than two years should get their BMD evaluated to determine whether they are experiencing significant losses.

Since 2004, when Pfizer submitted its data to the FDA, new studies have been published, confirming that the shot affects the BMD of different bones differently and can impact the women’s BMD at the spine and hip. These studies also show that the top of the thigh bone (known as the femoral neck) is particularly vulnerable to BMD loss in Depo users; this also the most common fracture site for post-menopausal women. The studies also confirm that longer-term use of Depo-Provera is associated with a greater amount of BMD loss. A 2006 study, funded by the National Institutes of Child Health and Human Development (NICHD), found that adult women’s hip BMD declined by 7.7 percent, and spine BMD declined by 6.4 percent, over four years of Depo use. In comparison, the BMD of women in the control group (who did not take Depo) declined < 1.6 percent and their spine BMD increased by .5 percent. Nearly 75 percent of the Depo users’ hip BMD loss, and 90 percent of their spine BMD loss, occurred in the first two years of using Depo.3

A 2008 study, which compared bone density, bone turnover, and hormones in matched pairs of 18–25-year-olds and 35–45 year-olds, found that Depo use was associated with a 5 percent bone density deficit at the spine and hip. The deficit was found in women who started using the shot before age 20, but not in those who started using it after age 34.4 After two years of Depo use, these women had lost about 5.7 percent of BMD at the lumbar spine and hip.5 A 2010 study found that, after two years of using Depo, almost half the women in the study (47.4 percent) had lost at least 5 percent of BMD at the spine or femoral neck. These women continued to experience significant BMD losses in the third year of Depo use as well. Between the second and third year of using Depo, the women experienced an average increased BMD loss at the spine from 5.3 percent to 5 percent, and at the femoral neck from 5.7 percent to 7.7 percent.6 As noted, the femoral neck is a vulnerable site for hip fracture, so continued low BMD there is concerning.

Reversal

Osteoporosis and bone fracture are commonly problems for older women who have already gone through menopause and are no longer using contraceptives. So, if women who stop getting contraceptive shots were found to recover the BMD they had lost, it would be reassuring. Unfortunately, the research on this point is contradictory. Discontinuation of Depo is associated with BMD recovery among women in these studies, but not all studies have demonstrated complete recovery.7 The length of time recovery takes is associated with both the length of time the woman used the shot and the specific bone site, with the femoral neck and hip recovering more slowly than the spine.8,9,10 On average, adult women who use Depo have a BMD that is similar to that of non-Depo users within two to three years after stopping the injections.11,12,13,14 The process may take longer, however: the NICHD study estimated that, among women who use the shot for longer than a year,
it might take as long as 92 months (over 7 years) for them to regain their original BMD levels.\textsuperscript{15}

After stopping Depo, women in one study regained an average of 2.4 percent of BMD annually at the spine; but femoral neck BMD loss recovered at a slower rate of 1.6 percent per year.\textsuperscript{16} The NICHD study found that, 18 months after stopping Depo, women who had used the method for two to three years had hip BMD that remained 4.7 percent below their baseline levels, and spine BMD levels 3.1 percent below baseline levels. Women in the control group had no change in their spine BMD and showed increased hip BMD.\textsuperscript{17}

Women may be able to reduce the risk of BMD loss associated with Depo by quitting smoking and increasing their calcium intake while using the shot, according to one recent study.\textsuperscript{18}

Research has not specifically explored the impact of any BMD loss on osteoporosis or fractures. Nor has research examined whether women’s bones might be more vulnerable after Depo use, in some way that is not measured by the BMD tests. Because the possible impact of BMD loss would occur many years in the future, its not clear what the full impact of Depo-related BMD loss may be on women’s health, or how menopause might impact BMD recovery.

**In Adolescents**

Although osteoporosis and bone fractures may be far off in the future for adolescent women, the issue of BMD loss and recovery is particularly important for them, as at least 90 percent of peak bone mass is developed by age 18.\textsuperscript{19} According to the U.S. Surgeon General, adolescent girls “experience their most rapid rate of bone growth during puberty and, by the end of puberty, they have almost achieved peak mass.”\textsuperscript{20} This context makes research showing that Depo users aged 18-to-21 experience greater loss and reduced acquisition of BMD than older women additionally troubling.\textsuperscript{21,22}

Depo’s impact on adolescent BMD loss appears to be more severe, probably because these young women are in the process of developing BMD. In studies of Depo users under age 21, BMD decreased in new Depo users at a rate of about 1.5 percent per year, while controls who were not taking Depo gained BMD at about two percent per year during the study. After two years of Depo use, these studies found differences in BMD of up to 6.8 percent between Depo users and non-users.\textsuperscript{23} A 2008 study, funded by the National Institutes of Health (NIH), found that adolescents taking Depo had spine BMD loss of 1.5 percent and femoral neck BMD loss of 5.2 percent after two years of use. The control group, whose members did not take Depo, had increased spine BMD of 6.3 percent, and femoral neck BMD of 3.5 percent, after two years.\textsuperscript{24} A 2010 study that followed adolescents aged 12-18 for seven years found that over half (53 percent) of young women taking Depo had BMD declines of more than 5 percent. Young women who experienced more BMD losses had received a greater number of Depo injections, on average, compared to young women with less BMD loss.\textsuperscript{25}

These studies indicate that use of DMPA by adolescent women results in BMD loss precisely at the time when bone growth and mineral accrual should be occurring.\textsuperscript{26} A 2005 study of adolescents funded by the NIH found that 14-to-18-year-old-Depo users experienced enough BMD loss that it could significantly raise their risk of experiencing a bone fracture.\textsuperscript{27} In 2008, the American Society for Reproductive Medicine’s Practice Committee noted that “the preponderance of evidence is that the use of Depo before a woman attains peak bone mass is detrimental to bone” and may prevent adolescents from achieving peak bone mass.\textsuperscript{28}

Adolescent women appear to recover BMD when they discontinue use of Depo, although recovery occurs more slowly than in adults and more slowly with an increased number of shots.\textsuperscript{29,30}

In the 2005 NIH study, a year or more after they stopped using the shot, young women’s BMD measurements were at least as high as those of the women in the control group.\textsuperscript{31} Again, researchers found variation based on location of the bone tested. A longitudinal study on adolescents published in 2010 found that BMD began increasing soon after the women stopped using Depo, and recovery occurred faster at the spine than the hip or femoral neck.\textsuperscript{32} BMD lev-
els at the hip recovered most slowly and did not return to baseline levels for almost five years.

**Concerns**
The National Women’s Health Network (NWHN) values the research on Depo’s safety and the availability of accurate information about the method’s side effects. Yet, the NWHN and other reproductive rights advocates remain concerned about the motivation behind the FDA’s label warnings. Unfortunately, under the Bush Administration, the FDA developed a pattern of manipulating or suppressing scientific data for conservative political ends and attacking family planning and reproductive choice.

The “black box” warning that was added to the Depo label in 2004 is the FDA’s most severe label warning and is typically reserved for life-threatening conditions. Depo’s effects on BMD are much less severe than the effects that typically drive such a warning. This disparity and the FDA’s unfortunate recent history raise questions about whether the Depo-Provera warning reflects a sincere effort to protect women’s health and share new scientific evidence, or a politically motivated attack on contraception and advancement of an anti-choice agenda.

Several expert organizations have not incorporated the FDA warnings into their guidelines for the shot. The Society for Adolescent Medicine’s Depo-Provera guidelines state that the duration of use does not need to be restricted to two years; the World Health Organization’s (WHO) and American College of Obstetricians and Gynecologists’ (ACOG) guidelines do not place any restrictions on the length of Depo use in women aged 18-45. The Practice Committee of the American Society for Reproductive Medicine does not recommend BMD testing of Depo users. The fact that such expert organizations have chosen not to reinforce the FDA warnings heightens suspicions about the FDA’s motive in requiring the “black box” label.

The length of time it takes a woman’s bone mineral density to recover after using the shot makes it important to weigh the method’s use carefully, particularly for young women (whose BMD is still developing) and women approaching menopause (who are at greater risk for osteoporosis and fractures). Women must consider whether the shot offers enough benefits to outweigh the possible risk posed to their bone mineral density and future health. Women who have existing risk factors for osteoporosis — metabolic bone disease, chronic alcohol or tobacco use, anorexia nervosa, or chronic use of anticonvulsants or corticosteroids (which can also reduce BMD) — should be especially cautious about using Depo.

As a long-acting, hormonal contraceptive method, Depo-Provera has advantages and disadvantages that each woman must assess with respect to her own life circumstances and health status. Depo’s effect on BMD increases the need for women to receive thorough counseling and comprehensive education in order to make a fully informed decision about whether or not to use the shot, and for how long. Further research is needed to determine which women, if any, are most likely to experience irreversible BMD loss, and the full impact of any adolescent BMD loss on future fractures and/or osteoporosis.

**Contact Us**
The National Women’s Health Network is committed to ensuring that women have access to accurate, balanced information. For more information, email us at healthquestions@nwhn.org or call the Women’s Health Voice at (202) 682-2646. Stay informed, connect with us on Facebook and Twitter.

**References**
4. Walsh J, Eastell E, Peel N, “Effects of Depot Medroxyprogesterone Acetate on Bone Density and
Bone Metabolism before and after Peak Bone Mass: A Case-Control Study," Journal of Clinical Endocrinology & Metabolism 2008; 93:1317-1323.


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